NDA 21-071/S-002

JUL 11 2000

SmithKline Beecham Corporation
Attention: Sharon W. Shapowal, RPh
One Franklin Plaza
200 N. 16th Street
Philadelphia, PA 19102

Dear Ms. Shapowal:

Please refer to your supplemental new drug application dated October 27, 1999, received October 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandia® (rosiglitazone maleate) Tablets, 2 mg, 4 mg, and 8 mg.

We acknowledge receipt of your submission dated June 14, 2000.

This supplemental new drug application provides for revisions to the Edema subsection of the PRECAUTIONS section of the package insert labeling. The following paragraph was added:

> "Since thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure, patients at risk for heart failure (particularly those on insulin) should be monitored for signs and symptoms of heart failure (See PRECAUTIONS, Use in Patients with Heart Failure)."

This labeling was submitted as an CBE and was in implemented on November 5, 1999. The FPL submitted (dated October 27, 1999), was compared to the labeling that was approved for this supplement (labeling dated April 3,2000); no other revisions were made.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted October 27, 1999. Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

AV:L2

PRESCRIBING INFORMATION

AVANDIA®

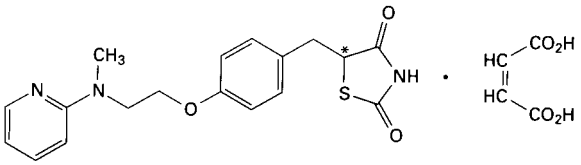
brand of
rosiglitazone maleate tablets

DESCRIPTION

Avandia (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. *Avandia* is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). *Avandia* improves glycemic control while reducing circulating insulin levels.

Pharmacological studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The structural formula is:



rosiglitazone maleate

The molecular formula is $C_{18}H_{19}N_3O_3S \bullet C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Each pentagonal film-coated Tiltab® tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are: hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and one or more of the following: synthetic red and yellow iron oxides and talc.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat. Rosiglitazone also prevents the development of overt diabetes in both the db/db mouse and Zucker fa/fa Diabetic Fatty rat models.

In animal models, rosiglitazone's antidiabetic activity was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

Pharmacokinetics and Drug Metabolism

Maximum plasma concentration (Cmax) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (Table 1). The elimination half-life is 3 to 4 hours and is independent of dose.

Table 1. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (N=32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
$AUC_{0\text{-inf}}$ [ng.hr./mL]	358 (112)	733 (184)	2971 (730)	2890 (795)
C_{max} [ng/mL]	76 (13)	156 (42)	598 (117)	432 (92)
Half-life [hr.]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F* [L/hr.]	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

*CL/F = Oral Clearance.

Absorption
The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease in C_{max} and a delay in T_{max} (1.75 hours). These changes are not likely to be clinically significant; therefore, *Avandia* (rosiglitazone maleate) may be administered with or without food.

Distribution
The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Metabolism
Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone.

In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P_{450} (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

Excretion
Following oral or intravenous administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103 to 158 hours.

Population Pharmacokinetics in Patients with Type 2 Diabetes
Population pharmacokinetic analyses from three large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

Special Populations
Age: Results of the population pharmacokinetic analysis (n=716 <65 years; n=331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Gender: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (n=405) was approximately 6% lower compared to male patients of the same body weight (n=642).

As monotherapy and in combination with metformin, *Avandia* improved glycemic control in both males and females. In metformin combination studies, efficacy was demonstrated with no gender differences in glycemic response.

In monotherapy studies, a greater therapeutic response was observed in females; however, in more obese patients, gender differences were less evident. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target PPARγ is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to *Avandia* in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Hepatic Impairment: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Therapy with Avandia (rosiglitazone maleate) should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline (see PRECAUTIONS, *Hepatic Effects*).

Renal Impairment: There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving *Avandia*. Since metformin is contraindicated in patients with renal impairment, co-administration of metformin with *Avandia* is contraindicated in these patients.

Race: Results of a population pharmacokinetic analysis including subjects of Caucasian, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

Pediatric Use: The safety and effectiveness of *Avandia* in pediatric patients have not been established.

Pharmacodynamics and Clinical Effects

In clinical studies, treatment with *Avandia* resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c), with a concurrent reduction in insulin and C-peptide. Postprandial glucose and insulin were also reduced. This is consistent with the mechanism of action of *Avandia* as an insulin sensitizer. The improvement in glycemic control was durable, with maintenance of effect for 52 weeks. The maximum recommended daily dose is 8 mg. Dose-ranging studies suggested that no additional benefit was obtained with a total daily dose of 12 mg.

The addition of *Avandia* to metformin resulted in significant reductions in hyperglycemia compared to either of the agents alone. These results are consistent with a synergistic effect of *Avandia* plus metformin combination therapy on glycemic control.

Reduction in hyperglycemia was associated with increases in weight. In the 26-week clinical trials, the mean weight gain in patients treated with *Avandia* was 1.2 kg (4 mg daily) to 3.5 kg (8 mg daily) when administered as monotherapy and 0.7 kg (4 mg daily) and 2.3 kg (8 mg daily) when administered in combination with metformin. A mean weight loss of about 1 kg was seen for both placebo and metformin alone in these studies. In the 52-week glyburide-controlled study, there was a mean weight gain of 1.75 kg to 2.95 kg for patients treated with 4 mg and 8 mg of *Avandia* daily, respectively, versus 1.9 kg in glyburide-treated patients.

Patients with lipid abnormalities were not excluded from clinical trials of *Avandia*. In all 26-week controlled trials, across the recommended dose range, *Avandia* as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls (Table 2).

Increases in LDL occurred primarily during the first 1 to 2 months of therapy with *Avandia* and LDL levels remained elevated above baseline throughout the trials. In contrast, HDL continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of therapy and then appeared to decrease over time. Because of the temporal nature of lipid changes, the 52-week glyburide-controlled study is most pertinent to assess long-term effects on lipids. At baseline, week 26, and week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0, respectively, for *Avandia* 4 mg twice daily. The corresponding values for glyburide were 3.2, 3.1, and 2.9. The differences in change from baseline between *Avandia* and glyburide at week 52 were statistically significant.

The pattern of LDL and HDL changes following therapy with *Avandia* in combination with metformin were generally similar to those seen with *Avandia* in monotherapy.

The changes in triglycerides during therapy with Avandia (rosiglitazone maleate) were variable and were generally not statistically different from placebo or glyburide controls.

Table 2. Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week Glyburide-Controlled Monotherapy Studies

	Placebo-controlled Studies Week 26			**Glyburide-controlled Study Week 26 and Week 52**			
		Avandia		**Glyburide titration**		***Avandia* 8 mg**	
	Placebo	**4 mg daily***	**8 mg daily***	**Wk 26**	**Wk 52**	**Wk 26**	**Wk 52**
Free Fatty Acids							
N	207	428	436	181	168	166	145
Baseline (mean)	18.1	17.5	17.9	26.4	26.4	26.9	26.6
% Change from base-line (mean)	+0.2%	–7.8%	–14.7%	–2.4%	–4.7%	–20.8%	–21.5%
LDL							
N	190	400	374	175	160	161	133
Baseline (mean)	123.7	126.8	125.3	142.7	141.9	142.1	142.1
% Change from base-line (mean)	+4.8%	+14.1%	+18.6%	–0.9%	–0.5%	+11.9%	+12.1%
HDL							
N	208	429	436	184	170	170	145
Baseline (mean)	44.1	44.4	43.0	47.2	47.7	48.4	48.3
% Change from base-line (mean)	+8.0%	+11.4%	+14.2%	+4.3%	+8.7%	+14.0%	+18.5%

*Once daily and twice daily dosing groups were combined.

Clinical Studies

Monotherapy
A total of 2315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with *Avandia* as monotherapy in six double-blind studies, which included two 26-week placebo-controlled studies, one 52-week glyburide-controlled study, and three placebo-controlled dose-ranging studies of 8 to 12 weeks' duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week placebo run-in period prior to randomization.

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL and mean baseline HbA1c 8.9%), were conducted. Treatment with *Avandia* produced statistically significant improvements in FPG and HbA1c compared to baseline and relative to placebo (Table 3).

Table 3. Glycemic Parameters in Two 26-Week Placebo-Controlled Trials

	Placebo	***Avandia* 2 mg twice daily**	***Avandia* 4 mg twice daily**
STUDY A			
N	158	166	169
FPG (mg/dL)			
Baseline (mean)	229	227	220
Change from baseline (mean)	19	–38	–54
Difference from placebo (adjusted mean)		–58*	–76*
Responders (≥30 mg/dL decrease from baseline)	16 %	54%	64%
HbA1c (%)			
Baseline (mean)	9.0	9.0	8.8
Change from baseline (mean)	0.9	–0.3	–0.6
Difference from placebo (adjusted mean)		–1.2*	–1.5*
Responders (≥0.7% decrease from baseline)	6%	40%	42%

	Placebo	*Avandia* 4 mg once daily	*Avandia* 2 mg twice daily	*Avandia* 8 mg once daily	*Avandia* 4 mg twice daily
STUDY B					
N	173	180	186	181	187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference From placebo (adjusted mean)	-	-31*	-43*	-49*	-62*
Responders (≥30 mg/dL decrease from baseline)	19%	45%	54%	58%	70%
HbA1c (%)					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference From placebo (adjusted mean)	-	-0.8*	-0.9*	-1.1*	1.5*
Responders (≥ 0.7 decrease from baseline)	9%	28%	29%	39%	54%

* <0.0001 compared to placebo.

When administered at the same total daily dose, *Avandia* was generally more effective in reducing FPG and HbA1c when administered in divided doses twice daily compared to once daily doses. However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice daily doses was not statistically significant.

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were randomized to treatment with Avandia (rosiglitazone maleate) 2 mg twice daily (N=195) or *Avandia* 4 mg twice daily (N=189) or glyburide (N=202) for 52 weeks. Patients receiving glyburide were given an initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in
2.5 mg/day increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize glycemic control. Thereafter the glyburide dose was kept constant.

The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (Figures 1 and 2). At the end of week 52, the reduction from baseline in FPG and HbA1c was –40.8 mg/dL and –0.53% with *Avandia* 4 mg twice daily; –25.4 mg/dL and –0.27% with *Avandia* 2 mg twice daily; and –30.0 mg/dL and –0.72% with glyburide. For HbA1c, the difference between *Avandia* 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with *Avandia*; however, this effect was less durable over time. The improvement in glycemic control seen with *Avandia* 4 mg twice daily at week 26 was maintained through week 52 of the study.

Figure 1. Mean FPG Over Time in a 52-Week Glyburide-Controlled Study

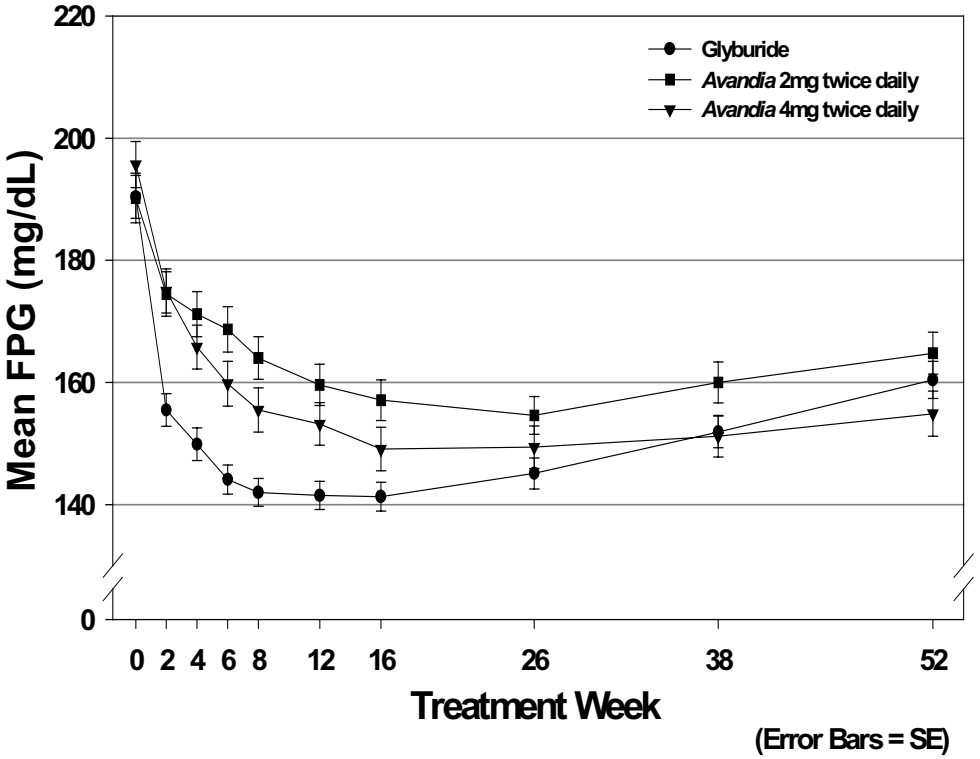
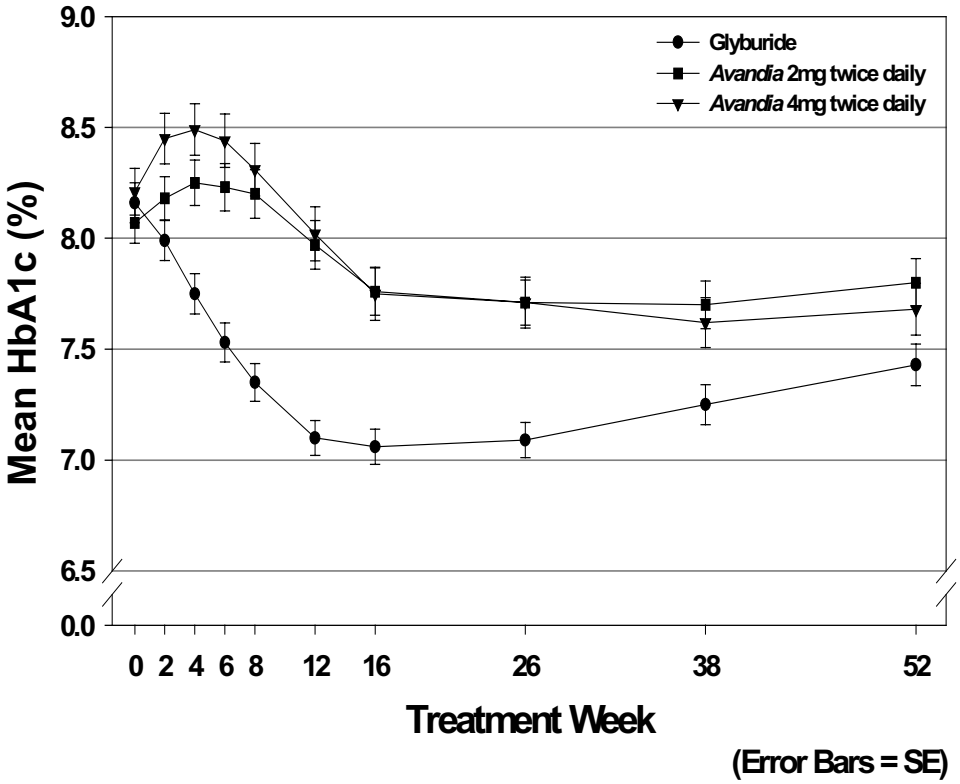


Figure 2. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Study



Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5% (2 mg twice daily) and 1.6% (4 mg twice daily) of patients treated with *Avandia*. The improvements in glycemic control were associated with a mean weight gain of 1.75 kg and 2.95 kg for patients treated with 2 mg and 4 mg twice daily of *Avandia*, respectively, versus 1.9 kg in glyburide-treated patients. In patients treated with *Avandia*, C-peptide, insulin, pro-insulin, and pro-insulin split products were significantly reduced in a dose-ordered fashion, compared to an increase in the glyburide-treated patients.

Combination with Metformin

A total of 670 patients with type 2 diabetes participated in two 26-week, randomized, double-blind, placebo/active-controlled studies designed to assess the efficacy of Avandia (rosiglitazone maleate) in combination with metformin. *Avandia*, administered in either once daily or twice daily dosing regimens, was added to the therapy of patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin.

In one study, patients inadequately controlled on 2.5 grams/day of metformin (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive *Avandia* 4 mg once daily, *Avandia* 8 mg once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and HbA1c was observed in patients

treated with the combinations of metformin and *Avandia* 4 mg once daily and *Avandia* 8 mg once daily, versus patients continued on metformin alone (Table 4).

Table 4. Glycemic Parameters in a 26-Week Combination Study

	Metformin	***Avandia* 4 mg Once daily +metformin**	***Avandia* 8 mg once daily +metformin**
N	113	116	110
FPG (mg/dL)			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
Difference from placebo (adjusted mean)		-40*	-53*
Responders (≥30 mg/dL decrease from baseline)	20%	45%	61%
HbA1c (%)			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	-0.6	-0.8
Difference from placebo (adjusted mean)		-1.0*	-1.2*
Responders (≥0.7% decrease from baseline)	11%	45%	52%

*<0.0001 compared to metformin.

In a second 26-week study, patients with type 2 diabetes inadequately controlled on 2.5 grams/day of metformin who were randomized to receive the combination of *Avandia* 4 mg twice daily and metformin (N=105) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of –56 mg/dL and a mean treatment effect for HbA1c of –0.8% over metformin alone. The combination of metformin and *Avandia* resulted in lower levels of FPG and HbA1c than either agent alone.

Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with *Avandia* demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c. In this group, increases in LDL and VLDL were also seen.

INDICATIONS AND USAGE

Avandia is indicated as monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Avandia is also indicated for use in combination with metformin when diet, exercise, and *Avandia* alone or diet, exercise, and metformin alone do not result in adequate glycemic control in patients with type 2 diabetes. For patients inadequately controlled with a maximum dose of metformin, *Avandia* should be added to, rather than substituted for, metformin.

Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with Avandia (rosiglitazone maleate), secondary causes of poor glycemic control, e.g., infection, should be investigated and treated.

CONTRAINDICATIONS
Avandia is contraindicated in patients with known hypersensitivity to this product or any of its components.

PRECAUTIONS
General
Due to its mechanism of action, *Avandia* is active only in the presence of insulin. Therefore, *Avandia* should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Ovulation: *Avandia*, like other thiazolidinediones, may result in resumption of ovulation in premenopausal, anovulatory women with insulin resistance. **As a consequence of their improved insulin sensitivity, these patients may be at risk for pregnancy if adequate contraception is not used.**

Although hormonal imbalance has been seen in preclinical studies (see Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with *Avandia* should be reviewed.

Hematologic: Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤1.0 gram/dL and ≤3.3%, respectively) were observed for both *Avandia* alone and in combination with metformin. The changes occurred primarily during the first 4 to 8 weeks of therapy and remained relatively constant thereafter. White blood cell counts also decreased slightly in patients treated with *Avandia*. The observed changes may be related to the increased plasma volume observed with treatment with Avandia and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Edema: *Avandia* should be used with caution in patients with edema. In a clinical study in healthy volunteers who received *Avandia* 8 mg once daily for 8 weeks, there was a

statistically significant increase in median plasma volume (1.8 mL/kg) compared to placebo.

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with *Avandia* (See ADVERSE REACTIONS).

Since thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure, patients at risk for heart failure (particularly those on insulin) should be monitored for signs and symptoms of heart failure (See PRECAUTIONS, *Use in Patients with Heart Failure).*

Use in Patients with Heart Failure: In preclinical studies, thiazolidinediones, including rosiglitazone, caused plasma volume expansion and pre-load-induced cardiac hypertrophy. Two ongoing echocardiography studies in patients with type 2 diabetes (a 52-week study with *Avandia* 4 mg twice daily [n=86] and a 26-week study with 8 mg once daily [n=90]), have shown no deleterious alteration in cardiac structure or function. These studies were designed to detect a change in left ventricular mass of 10% or more.

Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials. *Avandia* is not indicated in patients with NYHA Class 3 and 4 cardiac status unless the expected benefit is judged to outweigh the potential risk.

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, has been associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death have been reported during postmarketing clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT>3X upper limit of normal) compared to placebo, and very rare cases of reversible jaundice were reported.

In clinical studies in 4598 patients treated with *Avandia*, encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevation of ALT levels.

In controlled trials, 0.2% of patients treated with *Avandia* had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with *Avandia* were reversible and were not clearly causally related to therapy with Avandia (rosiglitazone maleate).

Although available clinical data show no evidence of *Avandia*-induced hepatotoxicity or ALT elevations, rosiglitazone is structurally very similar to troglitazone, which has been associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death. Pending the availability of the results of additional large, long-term controlled clinical trials and postmarketing safety data following wide clinical use of *Avandia* to more fully define its hepatic safety profile, it is recommended that patients

treated with *Avandia* undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with *Avandia* in all patients. Therapy with *Avandia* should not be initiated in patients with increased baseline liver enzyme levels (ALT>2.5X upper limit of normal). In patients with normal baseline liver enzymes, following initiation of therapy with *Avandia*, it is recommended that liver enzymes be monitored every 2 months for the first 12 months, and periodically thereafter. Patients with mildly elevated liver enzymes (ALT levels one to 2.5X upper limit of normal) at baseline or during therapy with *Avandia* should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with *Avandia* in patients with mild liver enzyme elevations should proceed with caution and include appropriate close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X upper limit of normal in patients on therapy with *Avandia*, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with *Avandia* should be discontinued.

There are no data available to evaluate the safety of *Avandia* in patients who experience liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. *Avandia* should not be used in patients who experienced jaundice while taking troglitazone. For patients with normal hepatic enzymes who are switched from troglitazone to *Avandia*, a 1-week washout is recommended before starting therapy with *Avandia*.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with *Avandia* should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Laboratory Tests
Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response.

Liver enzyme monitoring is recommended prior to initiation of therapy with *Avandia* in all patients and periodically thereafter (See PRECAUTIONS, *Hepatic Effects* and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients
Patients should be informed of the following:

Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but in maintaining the efficacy of drug therapy.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and every 2 months for the first 12 months, and periodically thereafter. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.

Avandia can be taken with or without meals.

Use of *Avandia* may cause resumption of ovulation in premenopausal, anovulatory women with insulin resistance. Therefore, contraceptive measures may need to be considered.

Drug Interactions

Drugs Metabolized by Cytochrome P_{450}

In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P_{450} enzymes at clinically relevant concentrations. *In vitro* data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9.

Avandia (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinylestradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Glyburide: *Avandia* (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy.

Metformin: Concurrent administration of *Avandia* (2 mg twice daily) and metformin (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state pharmacokinetics of either metformin or rosiglitazone.

Acarbose: Coadministration of acarbose (100 mg three times daily) for 7 days in healthy volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of *Avandia*.

Digoxin: Repeat oral dosing of *Avandia* (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

Warfarin: Repeat dosing with *Avandia* had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with *Avandia* (rosiglitazone maleate).

Ranitidine: Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the pharmacokinetics of either single oral or intravenous doses of rosiglitazone in healthy volunteers. These results suggest that the absorption of oral rosiglitazone is not altered in conditions accompanied by increases in gastrointestinal pH.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the *in vitro* bacterial assays for gene mutation, the *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo/in vitro* rat UDS assay. There was a small (about 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Animal Toxicology

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Morphometric

measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Pregnancy
Pregnancy Category C
There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose.

There are no adequate and well-controlled studies in pregnant women. Avandia (rosiglitazone maleate) should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Labor and Delivery
The effect of rosiglitazone on labor and delivery in humans is not known.

Nursing Mothers
Drug related material was detected in milk from lactating rats. It is not known whether *Avandia* is excreted in human milk. Because many drugs are excreted in human milk, *Avandia* should not be administered to a nursing woman.

ADVERSE REACTIONS
In clinical trials, approximately 4600 patients with type 2 diabetes have been treated with *Avandia*; 3300 patients were treated for 6 months or longer and 2000 patients were treated for 12 months or longer.

The incidence and types of adverse events reported in clinical trials of *Avandia* as monotherapy are shown in Table 5.

Table 5. Adverse Events (≥5% in Any Treatment Group) Reported by Patients in Double-blind Clinical Trials with *Avandia* as Monotherapy

	Avandia Monotherapy N = 2526	Placebo N = 601	Metformin N = 225	Sulfonylureas* N = 626
Preferred Term	**%**	**%**	**%**	**%**
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9

*Includes patients receiving glyburide (N=514), gliclazide (N=91) or glipizide (N=21).

There were a small number of patients treated with *Avandia* who had adverse events of anemia and edema. Overall, these events were generally mild to moderate in severity and usually did not require discontinuation of treatment with *Avandia*.

In double-blind studies, anemia was reported in 1.9% of patients receiving *Avandia* compared to 0.7% on placebo, 0.6% on sulfonylureas and 2.2% on metformin. Edema was reported in 4.8% of patients receiving *Avandia* compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. Overall, the types of adverse experiences reported when *Avandia* was used in combination with metformin were similar to those during monotherapy with *Avandia*. Reports of anemia (7.1%) were greater in patients treated with a combination of *Avandia* and metformin compared to monotherapy with *Avandia*.

Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies (see Laboratory Abnormalities, Hematologic).

Laboratory Abnormalities

Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in patients treated with *Avandia* (mean decreases in individual studies up to 1.0 gram/dL hemoglobin and up to 3.3% hematocrit). The time course and magnitude of decreases were similar in patients treated with a combination of *Avandia* and metformin or monotherapy. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. White blood cell counts also decreased slightly in patients

treated with *Avandia*. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with *Avandia*.

Lipids: Changes in serum lipids have been observed following treatment with *Avandia* (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

Serum Transaminase Levels: In clinical studies in 4598 patients treated with Avandia (rosiglitazone maleate) encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels.

In controlled trials, 0.2% of patients treated with *Avandia* had reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with *Avandia* compared with 0.9% treated with placebo and 1% in patients treated with active comparators.

In the clinical program including long-term, open-label experience, the rate per 100 patient years exposure of ALT increase to >3X the upper limit of normal was 0.35 for patients treated with *Avandia*, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (See PRECAUTIONS, *Hepatic Effects*).

DOSAGE AND ADMINISTRATION

The management of antidiabetic therapy should be individualized.

Monotherapy

The usual starting dose of *Avandia* is 4 mg administered either as a single dose once daily or in divided doses twice daily. For patients who respond inadequately following 12 weeks of treatment as determined by reduction in FPG, the dose may be increased to 8 mg administered as a single dose once daily or in divided doses twice daily. Reductions in glycemic parameters by dose and regimen are described under CLINICAL PHARMACOLOGY, Clinical Efficacy. In clinical trials, the 4 mg twice daily regimen resulted in the greatest reduction in FPG and HbA1c.

Combination Therapy with Metformin

The usual starting dose of *Avandia* in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. The dose of *Avandia* may be increased to 8 mg/day following 12 weeks of therapy if there is insufficient reduction in FPG. *Avandia* may be administered as a single daily dose in the morning, or divided and administered in the morning and evening.

Avandia may be taken with or without food.

No dosage adjustments are required for the elderly.

No dosage adjustment is necessary when *Avandia* is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and *Avandia* is also contraindicated in patients with renal impairment.

Therapy with *Avandia* should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X the upper limit of normal at start of therapy) (See PRECAUTIONS, *Hepatic Effects* and CLINICAL PHARMACOLOGY, Hepatic Impairment). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with *Avandia* and periodically thereafter (See PRECAUTIONS, *Hepatic Effects*).

There are no data on the use of *Avandia* in patients under 18 years of age; therefore, use of *Avandia* in pediatric patients is not recommended.

OVERDOSAGE

Limited data are available with regard to overdosage in humans. In clinical studies in volunteers, Avandia (rosiglitazone maleate) has been administered at single oral doses of up to 20 mg and was well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

HOW SUPPLIED

Tablets: Each pentagonal film-coated Tiltab® tablet contains rosiglitazone as the maleate as follows: 2 mg–pink, debossed with SB on one side and 2 on the other;
4 mg–orange, debossed with SB on one side and 4 on the other; 8 mg–red-brown, debossed with SB on one side and 8 on the other.

2 mg bottles of 30: NDC 0029-3158-13
2 mg bottles of 60: NDC 0029-3158-18
2 mg bottles of 100: NDC 0029-3158-20
2 mg bottles of 500: NDC 0029-3158-25
2 mg SUP 100s: NDC 0029-3158-21

4 mg bottles of 30: NDC 0029-3159-13
4 mg bottles of 60: NDC 0029-3159-18
4 mg bottles of 100: NDC 0029-3159-20
4 mg bottles of 500: NDC 0029-3159-25
4 mg SUP 100s: NDC 0029-3159-21

8 mg bottles of 30: NDC 0029-3160-13
8 mg bottles of 100: NDC 0029-3160-20
8 mg bottles of 500: NDC 0029-3160-25
8 mg SUP 100s: NDC 0029-3160-21

STORAGE
Store at 25°C (77°F); excursions 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container.

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 R_X only

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